

Proportion of Breast Cancer Cases in the United States Explained by Well-Established Risk Factors

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Background: Few estimates of the fraction of cases of breast cancer attributable to recognized risk factors have been published. All estimates are based on selected groups, making their generalizability to the U.S. population uncertain. **Purpose:** Our goal was to estimate the fraction of breast cancer cases in the United States attributable to well-established risk factors (i.e., later age at first birth, nulliparity, higher family income, and first-degree family history of breast cancer), using data from the first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS), the survey and follow-up of a probability sample of the U.S. population. **Methods:** From a cohort of 7508 female participants surveyed in the early 1970s, and followed up between 1982 and 1984 and again in 1987, 193 breast cancer cases were accrued for study. We calculated incidence rates, relative risks (RRs), and population attributable risks (PARs) for breast cancer risk factors and extended our results to the U.S. female population by using sample weights from the NHANES I survey. **Results:** Our PAR estimates suggest that later age at first birth and nulliparity accounted for a large fraction of U.S. breast cancer cases, 29.5% (95% confidence interval [CI] = 5.6%-53.3%); higher income contributed 18.9% (95% CI = -4.3% to 42.1%), and family history of breast cancer accounted for 9.1% (95% CI = 3.0%-15.2%). Taken together, these well-established risk factors accounted for approximately 47% (95% CI = 17%-77%) of breast cancer cases in the NHEFS cohort and about 41% (95% CI = 2%-80%) in the U.S. population. **Conclusions:** The RRs for most of these risk factors were modest, but their prevalence as a group was high, leading to estimates that suggest that a substantial proportion of breast cancer cases in the United States are explained by well-established risk factors. **Implications:** Elucidation of the determinants underlying recognized factors and study of other factors that may confer risk or protection are needed in efforts to advance understanding of breast cancer etiology and to aid in devising strategies for prevention. [J Natl Cancer Inst 1987;87:1681-5]

The fraction of breast cancer cases in the United States that cannot be "explained" by recognized risk factors, and thus the fraction potentially attributable to unidentified determinants, is uncertain. Because the attributable risk estimates for breast cancer that have been published were derived from studies of spe-

cial population groups, including volunteers (1), screening program participants (2,3), and younger women residing in regions with tumor registries (3), the generalizability of the findings is questionable.

In this study, we estimate population attributable risks (PARs) for breast cancer for well-established risk factors (i.e., later age at first birth, nulliparity, higher family income, and first-degree family history of breast cancer). We used data from the prospective study (4) of a probability sample of the U.S. female population. To date, no such national estimates have been published.

Subjects and Methods

The study population was the cohort of women aged 25-74 years who participated in the first National Health and Nutrition Examination Survey (NHANES I). Participants were interviewed and medically examined from 1971 through 1975 to assess the health and nutritional status of the U.S. population (5,6). Certain groups thought to be at high risk of malnutrition, including women of childbearing age, the elderly, and the poor, were purposely oversampled. Sample weights applied to the NHANES I data, however, adjust the prevalence estimates of risk factors assessed between 1971 and 1975 for oversampling and nonresponse to the initial home interview and examination (7).

The NHANES I sample included 20 729 males and females aged 25-74 years, of whom 14 407 (70%) participated. These 14 407 subjects were subsequently traced for follow-up interviews between 1982 and 1984 and in 1987 as part of the NHANES I Epidemiologic Follow-up Study (NHEFS). Subjects aged 55 years and older at initial examination were also followed up in 1986. A primary goal of the follow-up study was to investigate the relationships of factors assessed in NHANES I, such as clinical, nutritional, and behavioral parameters, to subsequent morbidity and mortality. Of 8596 female participants, 91% were followed by personal or proxy questionnaire. The follow-up questionnaires collected information on health conditions, reproductive factors, and a variety of risk factors. Proxy interviews were conducted for deceased and incapacitated subjects. Hospital records were sought for subjects reporting a diagnosis of a malignancy during the follow-up interval, and death certificates were collected for decedents (8).

Of the 8596 female subjects enrolled in the NHEFS, we included 7508 in our analytic cohort. The 1088 excluded subjects encompass 271 with prior cancer or bilateral mastectomy, four with missing health history information, 800 lost to

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follow-up by questionnaire, and 13 with ambiguous information regarding breast cancer incidence.

The established risk factors selected for study are earlier age at menarche, nulliparity, later age at first full-term birth, later age at menopause, and history of breast cancer in a first-degree relative (4). We also assessed risk associated with family income as an indicator of socioeconomic status. History of benign breast disease as of 1971-1975 was not available for the cohort. Information on family income and age at menarche was obtained in the initial questionnaire. Data on age at first birth and age at menopause were obtained in the follow-up questionnaires and are treated as age-dependent variables, e.g., a woman who was nulliparous at the time of her base-line interview who gave birth during the follow-up period could contribute person-years at risk to more than one category of "age at first birth." Although information on family history of breast cancer was first collected in the 1982-1984 follow-up, this information was applied to the entire follow-up interval for relative risk (RR) and prevalence determinations.

Following exclusions, 193 subjects were classified as breast cancer cases, including subjects with supporting hospital records ($n = 147$; 146 coded as malignant, one coded as carcinoma in situ), death certificates ($n = 11$) and interview only ($n = 35$), as coded for the NHEFS public use data tapes (8).

Breast cancer incidence rates were computed for each risk factor. We calculated denominators by accumulating person-years at risk from the date of the initial medical examination to the date of diagnosis for breast cancer cases, to the date of death for deceased non-case subjects and to the date of last contact for living non-case subjects; numerators are the numbers of cases. These tabulations and incidence rates were calculated by use of the DATAB program of the EPICURE epidemiologic analysis package (9). Rates are expressed as the number of cases per 100 000 person-years at risk. To make rates comparable, we directly adjusted incidence rates by 10 age groups to the age distribution of subjects with information on family history and age at first birth (10).

RRs and 95% confidence intervals (CIs) were computed using a Poisson regression model in the AMFIT program of the EPICURE epidemiologic analysis package (9). Multiple regression analyses were conducted and included all risk factors presented in Table 1 plus age as a factor in the model, but, because there was little apparent confounding, the RRs presented in Table 1 are adjusted only for age (10 groups) in the Poisson models. Subjects with missing data for one or two of the three risk factors presented in Table 1 were included in separate categories in these analyses. The numbers in these indicator categories reflect the differences between the numbers of cases presented in Table 1 and the total of 193 cases and the difference between person-years included in Table 1 and the total of 98 382 person-years. A second approach was taken in which subjects with missing data were excluded, and multivariate RRs for Table 1 factors were similar.

The PAR is the percentage of all breast cancer cases attributable to the risk factor in question. Two PARs were estimated for each risk factor using a weighted sum approach. One PAR was for the NHEFS cohort itself and the other was estimated for the U.S. population, computed using NHEFS sample weights. PARs for the NHEFS were calculated by use of the following formulas:

$$PAR_j = (\text{overall rate}_j - \text{rate in unexposed}_j) / \text{overall rate}_j$$

$$PAR = \sum [\text{weight}_j \times PAR_j]$$

where j denotes an age group or other stratum and the weight is the proportion of cases in that stratum (11).

We obtained estimates of the PARs for the United States by applying stratum-specific incidence rates to risk factor prevalence estimates derived from the NHEFS for women in the United States. The formulas used for the PAR estimates for the United States were as follows:

$$PAR_j = (RR_j - 1) / (RR_j - 1 + (1/P_j))$$

$$PAR = \sum [\text{weight}_j \times PAR_j]$$

where RR_j is the incidence rate ratio of subjects with the risk factor in question (e.g., family history) to those without the risk factor, P_j is the prevalence of exposed subjects in the United States, and weight_j is the expected proportion of cases in stratum j based on the incidence rate.

Since the numbers of cases distributed into some of 10 age strata were low, and because adjusted RRs were similar, numbers of strata were reduced for both the NHEFS and U.S. PAR estimates: most PARs were computed using the four age groups presented in Table 2 as strata, except the PAR for family history, which used two levels of age (<50 years and ≥ 50 years), income, and age at first birth because of suggestions of different RRs across strata. Because the prevalence of family history of breast cancer was small (6.6%), however, and because stratum-specific case numbers again became sparse, we did not stratify income or age at first birth by family history of breast cancer in PAR calculations for these factors taken individually.

We calculated PARs for combinations of risk factors similarly to those for single risk factors, with the exposed group defined as subjects having any of the risk factors in question.

The variance estimates of the PARs were based on the assumption that the numbers of cases in each stratum follow independent Poisson distributions. Since the variability of the risk factor prevalence estimates in the United States was small compared with the variability of the U.S. incidence rate estimates derived from the NHEFS, the former was ignored in the PAR variance estimates. The 95% CIs for the PARs were calculated using the following formula: $PAR \pm (1.96 \times SD)$.

Results

The overall breast cancer incidence rate in the NHEFS cohort was 196 female case subjects per 100 000 female person-years, directly adjusted for comparability to the rates presented in Table 1. The corresponding rate for the NHEFS cohort adjusted for comparability to Surveillance, Epidemiology, and End Results (SEER) Program¹ rates for the 1970 U.S. standard population

Table 1. Breast cancer incidence rates and relative risks in the first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS) cohort

Risk category	Case frequency	Age-adjusted rate*	Age-adjusted relative risk† (95% confidence interval)
Age at first birth, y			
<20	35	136	1.0
20-29	97	203	1.5 (1.0-2.2)
>29	20	260	1.9 (1.1-3.3)
Nulliparous	34	259	1.8 (1.1-2.9)
Family history of breast cancer in a first-degree relative			
Negative	148	175	1.0
Positive	27	470	2.6 (1.7-3.9)
Income			
Lower third of the U.S. population	66	154	1.0
Upper two thirds of the U.S. population	120	259	1.7 (1.2-2.4)

*Internally age-adjusted incidence rates expressed as cases per 100 000 person-years.

†Relative risks and 95% confidence intervals computed by Poisson regression.

of men and women was 86.5 female cases per 100 000 person-years.

Age-adjusted incidence rates and RRs by age at first birth, history of breast cancer in a first-degree relative, and family income are presented in Table 1. Elevated rates were found for subjects who either had a first birth after age 19 years or who were nulliparous compared with women with a birth prior to age 20 and for those women with a family history of breast cancer. Income in the upper two thirds of the U.S. population was also found to increase risk compared with women with lower income. We found no consistent pattern of increasing risk with decreasing age at menarche. Age-adjusted RRs for ages at menarche at age 16 years or older and at ages 15, 14, 13, 12, and less than 12 years are 1.0, 1.5 (95% CI = 0.8-2.8), 1.1 (95% CI = 0.6-2.1), 1.2 (95% CI = 0.6-2.1), 1.2 (95% CI = 0.7-2.2), and 0.8 (95% CI = 0.4-1.7), respectively. Among menopausal women aged 45 years and older, menopause at age 45 years and older was found to increase risk (RR = 2.5, 95% CI = 1.3-5.1), compared with menopause before age 45 years, an effect that was similar in women aged 45-64 years and aged 65 years and older. A protective effect of prior bilateral oophorectomy was suggested in women over age 64 (RR = 0.7; 95% CI = 0.2-2.4). Among women aged 45 to 59 years, premenopausal status compared with menopause before age 45 years suggested increased risk (RR = 1.8; 95% CI = 0.6-5.7).

There was little confounding of any of the risk factors by one another, but there was a large group of subjects aged 45 years and older with unknown age at menopause (39% of case subjects and 29% of all person-years), due partly to unknown ovarian status in women with hysterectomy without bilateral oophorectomy, making it impossible to adequately assess poten-

tial confounding by age at menopause. The RR for the unknown age at menopause group compared with women with menopause before age 45 years was 3.4 (95% CI = 1.7-6.8).

Age-specific base-line rates and RRs are presented in Table 2. There were no statistically significant differences in the overall effects of these risk factors by age in a multiplicative model, but there was a suggestion that the effect of first-degree family history of breast cancer was greater in women younger than age 50 years than in women aged 50 years or older. Differences in the age-specific estimates for age at first birth and nulliparity were suggested, especially in women aged 65-69 years, although chance could have played a role, because this age group constitutes only 7% of person-years in the analytic cohort. The effect of higher income appeared to be greater in women aged 70 years and older.

Because of our limited sample size and similar distributions of age at first birth/nulliparity in the U.S. estimates and in the NHEFS cohort, and thus presumably similar average RRs, we combined all groups of women whose age at first birth was older than 19 years or who were nulliparous for PAR estimation. The RRs for family history of breast cancer and higher income combined and of family history and absence of early birth combined appeared to be less than multiplicative, although these suggestions of effect modification were not statistically significant: the RRs for family history of breast cancer alone, higher income alone, and their combination were 3.0 (95% CI = 1.5-5.9), 1.7 (95% CI = 1.2-2.5), and 3.3 (95% CI = 1.8-6.0), respectively. For the risk factors of absence of early birth alone, of family history alone, and their combination, the RRs were 1.6 (95% CI = 1.1-2.4), 3.2 (95% CI = 1.3-7.8), and 3.8 (95% CI = 2.2-6.9).

Table 2. Age-specific breast cancer incidence rates* and relative risks† (RRs) in the first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS) cohort

Age at diagnosis, y	Rate for no family history of breast cancer	RR for family history of breast cancer in a first-degree relative (95% confidence interval [CI])		
30-49	95	3.7 (1.6-8.2)		
50-64	179	2.5 (1.1-5.5)		
65-69	194	1.8 (0.4-8.3)		
≥70	348	2.4 (1.3-4.6)		
Age at diagnosis, y	Rate for age at first birth younger than 20 y	RR for first birth at age 20-29 y (95% CI)	RR for first birth at age 30 y or older (95% CI)	RR for nulliparity (95% CI)
30-49	83	1.4 (0.7-2.8)	2.7 (0.9-8.3)	1.0 (0.3-3.4)
50-64	97	2.3 (0.9-5.5)	0.5 (0.1-4.5)	3.6 (1.3-10.0)
65-69	308	0.8 (0.3-2.4)	0.4 (0.0-3.2)	0.5 (0.1-2.5)
≥70	246	1.5 (0.7-2.9)	3.0 (1.4-6.6)	1.9 (0.9-4.1)
Age at diagnosis, y	Rate for subjects with family income in lower third of U.S. females	RR for higher income (95% CI)		
30-49	87	1.3 (0.7-2.7)		
50-64	156	1.3 (0.7-2.6)		
65-69	191	1.3 (0.5-3.5)		
≥70	284	2.3 (1.5-3.6)		

*Rates are expressed as cases per 100 000 person-years.

†RRs and 95% CIs computed by Poisson regression.

Because the U.S. estimate of women aged 45 years and older with protective early menopause was small (under 20%) and because the proportion of women with unknown age at menopause was substantial, we did not include age at menopause in our attributable risk computations.

The PAR estimates for the individual and combined risk factors in the NHEFS cohort and in the U.S. population are presented in Table 3. Based on our risk factor prevalence estimates drawn from the NHEFS, fully 90% of U.S. women appear to have at least one of the risk factors listed in Table 3. Estimated for the total U.S. population, among factors whose PARs we were able to assess, the reproductive variable "absence of a birth before age 20" accounted for the greatest proportion of breast cancer cases (29.5%; 95% CI = 5.6%-53.3%). Income contributed the second highest PAR (18.9%; 95% CI = -4.3% to 42.1%), while family history of breast cancer contributed 9.1% (95% CI = 3.0%-15.2%). The combined PAR for later age at first birth/nulliparity and family history was 36.9% (95% CI = 11.4%-62.3%). Including greater income with the other factors raised the combined PAR to 40.8% (95% CI = 1.6%-80.0%) for the United States and 46.7% (95% CI = 16.7%-76.7%) for the NHEFS.

Discussion

The overall breast cancer incidence rate in the NHEFS cohort from the early 1970s to 1987 is quite similar to that in the areas covered by the SEER program of population-based cancer registries from 1973 through 1988 (86.5 versus 91.5 cases per 100 000 person-years) (12). The RRs for the studied well-established risk factors were modest, but their prevalence as a group was high; thus, the overall PAR is substantial. We estimate that about 41% of breast cancer cases in the United States were attributable to later age at first birth, nulliparity, family history of breast cancer, and higher socioeconomic status. Although it is possible that the apparent increased risk with higher income may be due to greater surveillance among wealthier women, we obtained a similar increased risk when we limited the follow-up

to the years before 1981 when routine screening mammography was less prevalent. The choice of "first birth before age 20 years" as the referent group for comparison of risks due to "later age at first birth" is somewhat arbitrary, assuming that there is a gradient of increased risk with age at first birth; thus, smaller PARs would probably result if we chose a referent group of "first birth before age 30 years," as in the American Cancer Society study of volunteers (1). Ascertainment of familial breast cancer history in more distant relatives, including the paternal line, may or may not increase the percent of breast cancer cases explained (13,14).

Several factors influence the reliability of this estimate. This study had a unique advantage in being able to estimate both the RRs of breast cancer associated with these risk factors and the prevalence of exposure to them using data from follow-up of a probability sample of U.S. women, allowing generalization to the nation. This effort also had two disadvantages. First, the confidence limits are wide for most of the U.S. PARs, given the modest accrual of breast cancer cases ($n = 193$), small referent groups, and loss of statistical efficiency due to the use of sample weights. Results for the NHEFS cohort are similar, however, and confidence limits are narrower. Second, two well-established risk factors, earlier age at menarche and prior benign breast disease, are not included in our analysis. Early age at menarche was not found to be a risk factor in this study. This is not surprising, since detection of small increases in risk over the restricted range of age at menarche in U.S. women can require a very large study. Information on the prevalence of prior benign breast disease was not collected at the start of follow-up.

While we could not directly assess the effects of earlier age at menarche and prior benign breast disease, using data from the Breast Cancer Detection Demonstration Project, we estimated that they are likely to add less than 15% to our overall PAR (3,15). If age at menarche was frequently misclassified, however, this could be an underestimate. Thus, 45%-55% of U.S. breast cancer cases may be explained by established factors, including these two. Risk associated with later menopause within the normal range may further increase the overall PAR, although a dose-response was not detected in this study. Ionizing radiation is also a recognized risk factor, but the percent of U.S. breast cancer cases attributable to background and medical radiation is estimated to be small: i.e., 2.4%, based on average doses in the United States published by the Committee on the Biologic Effects of Ionizing Radiation (BEIR V) (16) and risk coefficients derived from the Japanese atomic bomb survivor experience (Land CE: personal communication).

Recognition that half of U.S. breast cancer cases may not be attributable to these recognized factors, as well as the hope that modifiable factors can reduce recognized risks, supports current research directions. On the basis of international differences in breast cancer incidence rates and animal experiments, it has been hypothesized that high-fat diets increase breast cancer risk and are responsible for a substantial fraction of the disease. Increasingly sophisticated analytic studies, however, have failed to demonstrate an important role of total dietary fat in breast cancer etiology (4,17). Adult weight gain has been reported to increase breast cancer risk in postmenopausal women (18), but a better understanding is needed of the complex effects of weight

Table 3. Population attributable risk percents in the first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS) cohort and in the U.S. population

Risk factor	Population attributable risk (95% confidence interval)	
	NHEFS cohort	U.S. population
Later age at first birth or nulliparity	30.1 (8.9-51.4)	29.5 (5.6-53.3)
Income	22.6 (5.4-39.9)	18.9 (-4.3-42.1)
Family history of breast cancer in a first-degree relative*	8.1 (2.3-13.9)	9.1 (3.0-15.2)
Later age at first birth, nulliparity, or family history of breast cancer in a first-degree relative*	31.9 (5.1-58.6)	36.9 (11.4-62.3)
Later age at first birth, nulliparity, family history of breast cancer in a first-degree relative, or income	46.7 (16.7-76.7)	40.8 (1.6-80.0)

*Computed stratifying by two levels of income in addition to age strata because of a suggestion of different risks (effect modification) for family history of breast cancer by income.

on breast cancer risk by age and menopausal status, and the effects of diet in populations with wide ranges of dietary fat intake, of diet at a young age, and of other dietary factors. Alcohol consumption has been identified as a breast cancer risk factor, which if causal, could increase the percent of explained breast cancer cases (17).

Entirely new research directions also need to be explored. For decades breast cancer has been looked upon as a lifestyle disease and little attention has been given to occupational or environmental factors. While recent reports suggesting associations with organochlorine pesticide residues, polychlorinated biphenyls (PCBs), and electromagnetic fields may or may not be confirmed with further work, such leads should be aggressively pursued (19-21).

Ideally, knowledge of risk factors that may explain half of the most common malignancies among women would guide primary prevention efforts. The inability to alter these risk factors, however, has thus far limited their relevance for prevention. To use effectively what we do know about risk factors for this disease, current and future research should also focus on identification of the underlying biologic mechanisms. Thus, preventive strategies might be devised. Such elucidation of the underlying biology of breast cancer has begun to occur for familial risk with intense research activity centered on localization and isolation of inherited genes with germline mutations, such as BRCA1 and BRCA2 (22,23). Equal efforts should be expended to elucidate the biologic basis of the influence of childbearing, age at first birth, socioeconomic status, age at menarche, and age at menopause on breast cancer risk in human populations.

If the genetic, hormonal, and other biologic exposures and traits underlying breast cancer risk factors can be understood, these determinants may be responsible for a considerable part of the currently unexplained fraction of breast cancer cases as well.

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Notes

¹Editor's note: SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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